Etiology of Chronic Beryllium Disease

The Role of the Skin

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Definitions

- Etiology: The study of the origin or cause of disease.
- Palliate: To relieve without curing, to mitigate, alleviate symptoms.

- 1982; Heliobacter Pylori

The Beryllium Conundrum

- There is no dose/response relation between inhalation exposure and disease.
- Despite dramatic reduction in exposure workers still experience sensitization and CBD

Confounding Factors => Confounding Theories

- Different chemical forms (soluble/insoluble)
- Particle size vs. mass of exposure
- Genetic susceptibility / no “safe” exposure
- No suitable animal model

The “Corn Maze” strategy: re-evaluating our starting assumptions

- Back to the beginning- A review of the literature with a focus on the role of the skin in the development of Be sensitization
- Isocyanates, nickel, peanuts and latex

Entering the Maze

- The first cases of CBD were reported in 1946 (Hardy, Tabershaw) and were associated with penetrating wounds from broken glass using beryllium phosphors

- In the 1940's 100 cases of CBD and over 200 cases of acute pneumonitis associated with Be exposures in excess of 100ug/M^3 (TWA) and 400 ug/M^3 (STEL)

“The Epidemiology of Beryllium Intoxication” (Sterner,Eisenbud) 1951

- Studied 1900 workers at two plants over seven years (200 cases acute, 6 CBD)
- First to speculate that due to the lack of a dose/response relation, CBD may involve the immune system.
- Exceptional observation: “berylliosis develops only in individuals whose exposures have included the insoluble beryllium compounds, more specifically, beryllium oxide”.

Sterner and Eisenbud, perplexing factors

- Marked disparity between exposure and disease
- Compared to other industrial toxins, very low exposure causes fatal disease
- There can be a considerable delay or acute onset of disease after exposure
- Inability to reproduce disease in animals
- Disparate relation at autopsy between Be content in lungs and disease

Manifestations of Be disease

- Integument (skin, mucosal tissue)
  - Contact dermatitis, irritant/allergic
  - Be ulcer Be granulomas
  - Inflammatory lesions of skin and eyes
- Respiratory Tract
  - Rhinitis-tracheitis-bronchitis
  - Acute pneumonitis
  - Chronic pulmonary granulomatosis CBD

“Cutaneous Hypersensitivity Due to Beryllium” Curtis, 1951

- Performed the first skin patch testing on 13 patients with CBD; typical delayed allergic response.
- BeF2> BeSO4= BeCl2>>> Be metallic, BeO no response

- 8 of 16 control subjects became Be sensitized

“The Diagnosis of Beryllium Disease, with Special Reference to the Patch Test” Curtis 1959

- Demonstrated 32 of 32 positive response for patients with CBD
- No positives for patients with other lung disease

Complications with patch test

- Asymptomatic patients developed CBD shortly after screening with patch test
- Patch testing patients with CBD hastened disease progression
- Only soluble Be used for patch testing, insoluble Be, thought to be the cause of the disease, shows no response

“Discussion of Paper by Dr. Curtis” Dr. Byron Waksman (Harvard) 1959

- Without reservation, the hypersensitive state demonstrated by patch test is “*a generalized state affecting all tissue”.*
- The demonstrated skin reactions appear to “prove” the existence of “systemic hypersensitivity to beryllium ion in all types of beryllium disease”.
- Soluble forms of beryllium produce locally high antigen concentrations and produce acute disease but do not persist biologically

Dr. Waksman

- Non-soluble beryllium persist for long periods unaltered in tissue and produce the characteristic beryllium granuloma and Berylliosis.
- “Respiratory exposure may be a poor method of inducing delayed sensitivity”.
- “Insoluble beryllium, while capable of eliciting torpid reactions in sensitized persons, may themselves be quite incapable of inducing sensitization”

Dr. Waksman

- “Skin testing with soluble beryllium may be dangerous in a patient whose tissues contain beryllium if he does not yet have the disease”.
- Skin patch testing was discontinued in 1959

The Cardiff Case

- Only a single unique case of CBD was observed in 40 years
- The exposure at Cardiff was exclusively to insoluble beryllium
- The single case of CBD was due to a traumatic wound to the finger on a grinding wheel grossly contaminated with beryllium powder.
- The disease progressed from a finger ulcer, to skin granulomas (forearm) and to the lungs.

Denda & Woods

Back to the Start of the Maze

- Sterner and Eisenbud (1951) suggested that animals be first sensitized via a dermal exposure to soluble beryllium followed by chronic inhalation exposure to beryllium oxide.

- After 50 years, we could find no evidence that this experiment has ever been done nor has CBD been demonstrated in animals.

A Fun Conundrum

- You are hiking in the high Rockies when caught unprepared by a November blizzard. Three days later, tired, freezing and starving you come upon a cabin at dusk. Inside you find a match, a bed and canned food for cooking.
- There is an OIL LAMP, a STOVE and a FIREPLACE stacked with wood.

- Which do you light first?

Conclusions

- Immune system sensitization precedes development of CBD.
- The only proven method of invoking sensitization is via dermal exposure.
- There is no evidence that inhalation exposure only causes sensitization or CBD. (soluble or insoluble)

Research Questions

- Does ingestion/inhalation of soluble beryllium invoke tolerance?
- Can CBD be reproduced in animals using modified exposure protocols?
- Can strict control of surface contamination and skin exposure reduce disease?
- Isolation of workers to a single form of beryllium may be necessary.

And I

Thank You